TO-1542
(4-85)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ONLINE SEARCH REQUEST FORM

USER Mark P.-L.-H. SERIAL NUMBER 08/921,430

ART UNIT 3735 PHONE 308-2114 DATE 1/4/99

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).

Surgical sponges

machine readable information

barcode bar code

compressed symbology

(not much useable aside from inventor)

STAFF USE ONLY

COMPLETED 1-6-99
SEARCHER BP
ONLINE TIME 30 TOTAL TIME 35
(in minutes)
NO. OF DATABASES 3

SYSTEMS
✓ CAS ONLINE 68.99
___ DARC/QUESTEL
✓ DIALOG 59.89
___ SDC
___ OTHER

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=> file home
FILE 'HOME' ENTERED AT 15:21:08 ON 06 JAN 1999

=> display history full l1-

     (FILE 'HOME' ENTERED AT 13:29:55 ON 06 JAN 1999)
               SET HIGHLIGHTING ON

     FILE 'MEDLINE' ENTERED AT 13:30:06 ON 06 JAN 1999
               E SURGICAL SPONGES/CT
L1          1147 SEA "SURGICAL SPONGES"+NT/CT
               E AUTOMATIC DATA PROCESSING/CT
L2          6152 SEA "AUTOMATIC DATA PROCESSING"+NT/CT
L3             0 SEA L1 AND L2

     FILE 'WPIDS, BIOSIS, EMBASE, MEDLINE' ENTERED AT 13:32:49 ON 06 JAN
     1999
L4           254 SEA (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICA
                 L?)(3A)SPONG?
L5           148 SEA (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICA
                 L?)(3A)SPONG?
L6           146 SEA (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICA
                 L?)(3A)SPONG?
L7           410 SEA (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICA
                 L?)(3A)SPONG?
     TOTAL FOR ALL FILES
L8           958 SEA (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICA
                 L?)(3A) SPONG?

     FILE 'LCA' ENTERED AT 13:33:46 ON 06 JAN 1999
L9          5296 SEA DEVICE? OR CONTRIVANC? OR INVENTION? OR APPARAT? OR
                 APP## OR IMPLEMENT? OR INSTRUMENT? OR TOOL?
                 SET HIGHLIGHTING ON
L10          328 SEA EQUIP?
L11           40 SEA (AUTO OR AUTOMAT?)(2A)(ID OR IDS OR IDENTIF? OR
                 DATA#) OR MACHINE?(2A)(READ OR READS OR READING# OR
                 SCAN? OR INVENTORY? OR INVENTORIES) OR (ID OR IDS OR
                 IDENTIF?)(2A)(SYSTEM? OR METHOD? OR PROCEDUR? OR PLAN OR
                 PLANS OR PLANNED OR PLANNING# OR CONSTRUCT#)
L12            6 SEA BARCOD? OR (BAR OR BARS OR BARRED OR BARRING#)(2A)(CO
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L14       18276 SEA L11 OR L12
L15      219825 SEA L11 OR L12
L16       20760 SEA L11 OR L12
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L18          75 SEA COMPRESS?(2A)SYMBOL?
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L24             0 SEA L5 AND L14
L25            24 SEA L6 AND L15
L26             0 SEA L7 AND L16
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L28             0 SEA L4 AND L18
L29             0 SEA L5 AND L19
L30             0 SEA L6 AND L20
L31             0 SEA L7 AND L21
     TOTAL FOR ALL FILES
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L41             0 SEA L7 AND L36
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     FILE 'HOME' ENTERED AT 15:12:32 ON 06 JAN 1999

     FILE 'WPIDS' ENTERED AT 15:13:53 ON 06 JAN 1999

     FILE 'WPIDS, BIOSIS, EMBASE, MEDLINE' ENTERED AT 15:16:37 ON 06 JAN
     1999
L*** DEL    1528 FILE WPIDS
L*** DEL      30 FILE BIOSIS
L*** DEL      73 FILE EMBASE
L*** DEL      72 FILE MEDLINE
     TOTAL FOR ALL FILES
L*** DEL    1703 S MACHINE?(3A)(READAB? OR READEAB?)
L43          1542 SEA (MACHINE? OR SCANNER?)(3A)(READAB? OR READEAB?)
L44            30 SEA (MACHINE? OR SCANNER?)(3A)(READAB? OR READEAB?)
L45            73 SEA (MACHINE? OR SCANNER?)(3A)(READAB? OR READEAB?)
L46            72 SEA (MACHINE? OR SCANNER?)(3A)(READAB? OR READEAB?)
     TOTAL FOR ALL FILES
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titles and selected abstracts

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L47        1717 SEA (MACHINE? OR SCANNER?)(3A)(READAB? OR READEAB?)
L48           1 SEA L4 AND L43
L49           0 SEA L5 AND L44
L50           0 SEA L6 AND L45
L51           0 SEA L7 AND L46
     TOTAL FOR ALL FILES
L52           1 SEA L8 AND L47

     FILE 'WPIDS' ENTERED AT 15:20:43 ON 06 JAN 1999
L53           1 SEA L23 OR L48

     FILE 'HOME' ENTERED AT 15:21:08 ON 06 JAN 1999


     FILE HOME

     FILE MEDLINE
      FILE LAST UPDATED: 29 OCT 1998 (19981029/UP).  FILE COVERS 1966 TO

      MEDLINE UPDATES ON HOLD UNTIL AFTER THE ANNUAL RELOAD HAS BEEN
      COMPLETED.  NOTICE WILL BE GIVEN ONCE THE RELOAD IS COMPLETED AND
      RELOAD DETAILS WILL BE FOUND IN HELP RLOAD.

      THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
      SUBSTANCE IDENTIFICATION.

     FILE WPIDS
     FILE LAST UPDATED: 23 DEC 1998              <19981223/UP>
     >>>UPDATE WEEKS:
     MOST RECENT DERWENT WEEK            199851   <199851/DW>
     DERWENT WEEK FOR CHEMICAL CODING:   199846
     DERWENT WEEK FOR POLYMER INDEXING:  199848
     DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

     >>> D COST AND SET NOTICE DO NOT REFLECT SUBSCRIBER DISCOUNTS -
                                       SEE HELP COST FOR DETAILS <<<

     >>> INDEXING UPDATE CODES JUMP FORWARD TO 9901   -  SEE NEWS <<<

     FILE BIOSIS
     FILE COVERS 1969 TO DATE.
     CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
     FROM JANUARY 1969 TO DATE.

     RECORDS LAST ADDED: 22 December 1998 (19981222/ED)

     The BIOSIS file has been reloaded.  Enter HELP RLOAD and HELP REINDE
     for details.

     FILE EMBASE
      FILE COVERS 1974 TO 29 Dec 1998 (19981229/ED)
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This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE LCA
LCA IS A STATIC LEARNING FILE

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> file wpids
FILE 'WPIDS' ENTERED AT 15:22:04 ON 06 JAN 1999
COPYRIGHT (C) 1999 DERWENT INFORMATION LTD

FILE LAST UPDATED: 23 DEC 1998              <19981223/UP>
>>>UPDATE WEEKS:
MOST RECENT DERWENT WEEK            199851   <199851/DW>
DERWENT WEEK FOR CHEMICAL CODING:   199846
DERWENT WEEK FOR POLYMER INDEXING:  199848
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> D COST AND SET NOTICE DO NOT REFLECT SUBSCRIBER DISCOUNTS -
                                  SEE HELP COST FOR DETAILS <<<

>>> INDEXING UPDATE CODES JUMP FORWARD TO 9901   -  SEE NEWS <<<

=> d l53 1 iall
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(inventor)

```
L53  ANSWER 1 OF 1  WPIDS   COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER:     98-193847 [17]   WPIDS
DOC. NO. NON-CPI:     N98-153371
TITLE:                **Automatic identification
                    **system** accounting for **surgical
                    **sponges** during **surgery** - has
                    **machine readable** information on
                      substrate located on several **surgical
                    **sponges**, each **sponge** provides
                      unique information on it.
DERWENT CLASS:        S05 T04
INVENTOR(S):          STEWART, B E; STEWART, W W
PATENT ASSIGNEE(S):   (STEW-I) STEWART B E; (STEW-I) STEWART W W
COUNTRY COUNT:        77
PATENT INFORMATION:

     PATENT NO KIND DATE   WEEK   LA   PG  MAIN IPC
     ---------------------------------------------
     WO 9810367  A1 980312 (9817)* EN   15 G06K007-10
        RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL
            OA PT SD SE SZ UG ZW
         W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI
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GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT UA UG UZ VN YU ZW
AU 9741753 A 980326 (9832) G06K007-10

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9810367	A1	WO 97-US15413	970903
AU 9741753	A	AU 97-41753	970903

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9741753	A	Based on	WO 9810367

PRIORITY APPLN. INFO: US 96-25629 960904
INT. PATENT CLASSIF.:
MAIN: G06K007-10
BASIC ABSTRACT:
WO 9810367 A UPAB: 980428
The system accounts for and identifies several **surgical sponges** (10) used during a surgical procedure. **Machine readable** information (14) is located on the several **surgical sponges**. Each **sponge** has unique information on it and is for a particular one surgical procedure.

The information is located on a substrate (12) on the sponge, and each sponge includes an x-ray detectable element. The information can be within or on the sponge. There is human readable information on each sponge, associated with its respective unique **machine readable** information.

USE - For accounting for **sponges** used in **surgical** operation.

ADVANTAGE - Accounts for sponges in efficient and reliable manner and does not compromise on medical requirements.

Dwg.1/3
FILE SEGMENT: EPI
FIELD AVAILABILITY: AB; GI
MANUAL CODES: EPI: S05-G02; T04-A03B1

=> file embase
FILE 'EMBASE' ENTERED AT 15:22:22 ON 06 JAN 1999

FILE COVERS 1974 TO 29 Dec 1998 (19981229/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l25 1-24 ti

L25 ANSWER 1 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI 'Gossypiboma': An unusual cause of perinephric abscess.

L25 ANSWER 2 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Pseudotumour due to **surgical sponge**: Gossypiboma.

L25 ANSWER 3 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT of retained **surgical sponges** (textilomas): Pitfalls in detection and evaluation.

L25 ANSWER 4 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Retained **surgical sponge** after subtotal thyroidectomy [6].

L25 ANSWER 5 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT appearance of **surgical sponge** retained in pleura [1].

L25 ANSWER 6 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Appearance of oxidized cellulose (Surgicel) on postoperative CT scans: Similarity to postoperative abscess.

L25 ANSWER 7 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Magnetic resonance imaging of retained **surgical sponges**: Case report.

L25 ANSWER 8 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Sonography and computed tomography of a gossypiboma and in vitro studies of sponges by ultrasound: Case report.

L25 ANSWER 9 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Case report: MR appearance of a retained **surgical sponge**.

L25 ANSWER 10 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Pulmonary embolism caused by a **surgical sponge**.

L25 ANSWER 11 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Renal pseudotumor due to a retained perirenal sponge: CT features.

L25 ANSWER 12 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Gossypiboma in the early post-operative period: A diagnostic problem.

L25 ANSWER 13 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI The retained **surgical sponge** following intra-abdominal **surgery**: A continuing problem.

L25 ANSWER 14 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

TI Retained surgical gauzes: Acute and chronic CT and US findings.

L25 ANSWER 15 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Retained **surgical sponge** 40 years after laminectomy. Case report.

L25 ANSWER 16 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI [Intra-abdominal textiloma. Diagnostic value of ultrasound and CT scan imaging in 12 cases].
APPORT DE L'ECHOGRAPHIE ET DE LA SCANOGRAPHIE DANS LE DIAGNOSTIC DES TEXTILOMES INTRA-ABDOMINAUX. A PROPOS DE 12 CAS.

L25 ANSWER 17 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Retained **surgical sponge**: Diagnosis with CT and sonography.

L25 ANSWER 18 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT and ultrasound findings of **surgically** retained **sponges** and towels.

L25 ANSWER 19 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Retained **surgical sponges**: CT and US appearance.

L25 ANSWER 20 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI [The importance of US and CT in the detection of complications due to **surgical sponges** left in the abdomen].
UTILITA DEGLI US E DELLA TC NEL RICONOSCIMENTO DELLE COMPLIANZE DA GARZE RITENUTE NEL CAVO ADDOMINALE.

L25 ANSWER 21 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Identification of a retained **surgical sponge** using magnetic resonance imaging.

L25 ANSWER 22 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT appearance of a surgically retained towel (gossypiboma).

L25 ANSWER 23 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI MRI of a retained sponge in a dog.

L25 ANSWER 24 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Renal pseudotumors caused by retained pararenal **surgical sponges**.

=> d l25 3,5,7,8,9,16,17,18,21,22,23 ti so ab ct

L25 ANSWER 3 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT of retained **surgical sponges** (textilomas): Pitfalls in detection and evaluation.
SO Journal of Computer Assisted Tomography, (1996) 20/6 (919-923).
ISSN: 0363-8715 CODEN: JCATD5
AB Purpose: Our goal was to demonstrate possible pitfalls in the CT diagnosis of retained **surgical sponges**

(textilomas) and to evaluate the impact of gas bubbles inside a textiloma. Method: Thirteen patients with textilomas were investigated with CT 3 weeks to 8 years after surgery. Twelve of the 13 textilomas were removed within 3 weeks after the first CT examination. Eight samples of **surgical sponges** were placed in a water bath for 6 months. Serial CT was performed to document the presence and persistence of gas bubbles. Results: The radiopaque marker inside the textiloma was seen in nine patients but did not lead to the diagnosis in all patients. In seven patients gas bubbles were found inside the textiloma with a typical pattern. None of these patients had an abscess formation. In vitro studies demonstrated gas bubbles in all **surgical sponges** scanned 1 h afterward. The number of gas bubbles was not significantly reduced after 6 months. Conclusion: The variable appearance of retained **surgical sponges** can lead to diagnostic misinterpretations. If present, the typical spongiform pattern with gas bubbles is the most specific sign for the detection of textilomas but does not indicate an abscess formation.

CT EMTAGS: apparatus, equipment and supplies (0510); diagnosis (0140); **automation, computers and data processing** (0530); infection (0310); injury (0301); mammal (0738); human (0888); clinical article (0152); adolescent (0017); adult (0018); article (0060); priority journal (0007)

Medical Descriptors:
*sponge
*foreign body reaction: DI, diagnosis
computer assisted tomography
diagnostic imaging
abscess: DI, diagnosis
abdominal surgery
postoperative complication
foreign body: DI, diagnosis
human
clinical article
adolescent
adult
article
priority journal

L25 ANSWER 5 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

TI CT appearance of **surgical sponge** retained in pleura [1].

SO ACTA RADIOL., (1993) 34/2 (200).
ISSN: 0248-1851 CODEN: ACRAE3

CT EMTAGS: diagnosis (0140); injury (0301); apparatus, equipment and supplies (0510); **automation, computers and data processing** (0530); mammal (0738); human (0888); male (0041); case report (0151); aged (0019); priority journal (0007); letter (0008)

Medical Descriptors:
*coronary artery bypass surgery
*pleura disease: DI, diagnosis
*pleura disease: SU, surgery

*pleura disease: SI, side effect
*foreign body
*sponge
computer assisted tomography
human
male
case report
aged
priority journal
letter

L25 ANSWER 7 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Magnetic resonance imaging of retained **surgical sponges**: Case report.
SO CLIN. IMAGING, (1992) 16/4 (259-262).
ISSN: 0899-7071 CODEN: CLIMEB
AB The magnetic resonance imaging (MRI) features of sponges retained postsurgically in three patients are described. MRI depicted these as well-defined round masses, which were of low signal intensity on T1-weighted images and very high signal intensity on T2-weighted images. We scrutinized these masses on T2-weighted images. MRI revealed the low-signal-intensity structures to have wavy, striped, and/or spotted appearances, which raised the suspicion that they might be retained **surgical sponges** within mass lesions.
CT EMTAGS: diagnosis (0140); injury (0301); apparatus, equipment and supplies (0510); infection (0310); **automation, computers and data processing** (0530); diaphragm (0934); mammal (0738); human (0888); male (0041); case report (0151); aged (0019); adult (0018); article (0060)
Medical Descriptors:
*nuclear magnetic resonance imaging
*foreign body: DI, diagnosis
sponge
abscess: CO, complication
abscess: DI, diagnosis
diagnostic imaging
thorax disease: DI, diagnosis
computer assisted tomography
gastrectomy
nephrectomy
diaphragm
laparotomy
human
male
case report
aged
adult
article

L25 ANSWER 8 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Sonography and computed tomography of a gossypiboma and in vitro

studies of sponges by ultrasound: Case report.
SO CLIN. IMAGING, (1992) 16/4 (256-258).
ISSN: 0899-7071 CODEN: CLIMEB
AB A case of retained **surgical sponge** was imaged by ultrasound and computed tomography (CT). Sonography revealed a hypoechoic mass with areas of high echoes and acoustic shadowing. An experiment revealed that the high echoes were attributed partly to the presence of numerous interfaces of sponges. The sonographic detection of a mass with high echoes casting acoustic shadows should alert radiologists to the possibility of retained **surgical sponges** even if there is no gas or calcification on CT scans.
CT EMTAGS: diagnosis (0140); **automation, computers and data processing** (0530); injury (0301); apparatus, equipment and supplies (0510); mammal (0738); human (0888); female (0042); case report (0151); adult (0018); article (0060)
Medical Descriptors:
*echography
*computer assisted tomography
*foreign body: DI, diagnosis
sponge
gas
calcification
laparotomy
human
female
case report
adult
article

L25 ANSWER 9 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Case report: MR appearance of a retained **surgical sponge.**
SO CLIN. RADIOL., (1992) 46/1 (66-67).
ISSN: 0009-9260 CODEN: CLRAAG
AB A case of a retained **surgical sponge** found in the retroperitoneum is presented with findings on magnetic resonance (MR) imaging, computed tomography (CT), ultrasonography (US) and angiography. Among all the performed modalities, a characteristic internal structure of the gauze granuloma was best visualized on MR imaging. If no radio-opaque marker is seen on plain radiography or CT, the folded fabric inner structure visualized on T2-weighted images can be a most important clue to the correct diagnosis of this iatrogenic mass.
CT EMTAGS: apparatus, equipment and supplies (0510); diagnosis (0140); injury (0301); retroperitoneum (0969); **automation, computers and data processing** (0530); mammal (0738); human (0888); female (0042); case report (0151); adult (0018); priority journal (0007); article (0060)
Medical Descriptors:
*sponge
*nuclear magnetic resonance imaging

*foreign body: DI, diagnosis
clinical feature
retroperitoneum
computer assisted tomography
echography
angiography
human
female
case report
adult
priority journal
article

L25 ANSWER 16 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI [Intra-abdominal textiloma. Diagnostic value of ultrasound and CT scan imaging in 12 cases].
APPORT DE L'ECHOGRAPHIE ET DE LA SCANOGRAPHIE DANS LE DIAGNOSTIC DES TEXTILOMES INTRA-ABDOMINAUX. A PROPOS DE 12 CAS.
SO J. RADIOL., (1988) 69/4 (243-251).
ISSN: 0242-3081 CODEN: JRMDAH
AB Feared by every surgeon, retained **surgical sponges** (or gossypiboma) are rare iatrogenic entities. Ultrasonography and computed tomography are very valuable, providing an immediate answer in the majority of cases. We report 12 cases of intra-abdominal retained surgical swabs. The ultrasonic pattern was made either of a large poorly echogenic mass with a hyperechogenic center and sharply delineated posterior acoustic shadow (7 cases) or of a large acoustic shadow posterior to a solitary highly echogenic area (4 cases). Computed tomography demonstrated either large peripherally enhanced cystic mass associated with serpiginous or spongiform central area (5 cases) or heterogeneous abcess-like fluid mass.
CT EMTAGS: diagnosis (0140); **automation, computers and data processing** (0530); clinical article (0152); human (0888); iatrogenic disease (0300)
Medical Descriptors:
*abdomen
*foreign body
*sponge
*echography
*computer assisted tomography

L25 ANSWER 17 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Retained **surgical sponge**: Diagnosis with CT and sonography.
SO AM. J. ROENTGENOL., (1988) 150/5 (1047-1050).
ISSN: 0361-803X CODEN: AJROAM
AB The diagnosis of a retained **surgical sponge** was made by CT and sonography in four patients. The plain abdominal radiograph was normal in all cases. In each of four cases of gauze granuloma, CT showed a well-defined round mass with a thick wall; internal heterogeneous densities with a wavy, striped, and/or spotted appearance; mottled calcifications; and gas bubbles.

Sonography disclosed a well-defined hypoechoic mass containing highly echogenic foci with a strong posterior shadow. In these cases, CT and sonographic findings, together with a history of surgery, permitted the correct preoperative diagnosis of a retained foreign body.

CT EMTAGS: diagnosis (0140); **automation, computers and data processing** (0530); adult (0018); case report (0151); human (0888); infection (0310); iatrogenic disease (0300); male (0041); female (0042)
Medical Descriptors:
*sponge
*echography
*computer assisted tomography
adult
*abdomen
*granuloma: SU, surgery

L25 ANSWER 18 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT and ultrasound findings of **surgically** retained **sponges** and towels.
SO J. COMPUT. ASSISTED TOMOGRAPHY, (1987) 11/6 (1003-1006).
ISSN: 0363-8715 CODEN: JCATD5
AB The CT and ultrasound features of retained sponges (gossypibomas) are described in six patients. They are well-circumscribed cystic masses without surrounding edema. The retained sponges or towels were correctly identified in only three cases. In the other three cases retained sponges were organized and lost their original configuration. Gas was seen in one case and calcification in two cases. Gossypibomas should be included in the differential diagnosis in all patients with a well-circumscribed systic mass in the abdomen and with a history of previous laparotomy.
CT EMTAGS: diagnosis (0140); **automation, computers and data processing** (0530); clinical article (0152); iatrogenic disease (0300); human (0888); peritoneum (0944)
Medical Descriptors:
*foreign body
*echography
*computer assisted tomography
gossypiboma
*sponge

L25 ANSWER 21 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI Identification of a retained **surgical sponge** using magnetic resonance imaging.
SO NEUROSURGERY, (1986) 18/4 (496-498).
CODEN: NRSRDY
AB The authors report a patient who had a spinal abscess due to a retained **surgical sponge**. Through the use of magnetic resonance imaging, the sponge was identified. Postoperative foreign body complications are discussed.
CT EMTAGS: priority journal (0007); central nervous system (0912); human (0888); iatrogenic disease (0300); diagnosis (0140); case

report (0151); **automation, computers and data processing** (0530)
Medical Descriptors:
*spinal cord abscess
*foreign body
*nuclear magnetic resonance imaging
sponge

L25 ANSWER 22 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI CT appearance of a surgically retained towel (gossypiboma).
SO J. COMPUT. ASSISTED TOMOGRAPHY, (1986) 10/2 (343-345).
CODEN: JCATD5
AB A case of a surgically retained towel within the peritoneal space is reported. Computed tomography demonstrated an unusual appearance not unlike that previously described for retained **surgical sponges**. Computed tomography of the gastrointestinal tract served as a useful adjunct to barium radiography in this case, suggesting the correct diagnosis of foreign body.
CT EMTAGS: priority journal (0007); peritoneum (0944); diagnosis (0140); **automation, computers and data processing** (0530); human (0888); aged (0019); iatrogenic disease (0300); digestive system (0935); therapy (0160); case report (0151)
Medical Descriptors:
*peritoneum
*gossypiboma
*computer assisted tomography

L25 ANSWER 23 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
TI MRI of a retained sponge in a dog.
SO MAGN. RESON. IMAGING, (1985) 3/3 (283-286).
CODEN: MRIMDQ
AB Retained sponges after laparotomy may cause a broad spectrum of clinical symptoms and present a difficult diagnostic problem. We report a case of retained **surgical sponge** in a dog to illustrate the MRI findings of this infrequent but important cause of postoperative complications.
CT EMTAGS: methodology (0130); nonhuman (0777); iatrogenic disease (0300); dog (0711); peritoneum (0944); animal experiment (0112); **automation, computers and data processing** (0530)
Medical Descriptors:
*nuclear magnetic resonance imaging
*surgical swab

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?show files
File   2:INSPEC 1969-1998/Dec W4
         (c) 1999 Institution of Electrical Engineers
File   8:Ei Compendex(R) 1970-1998/Jan W1
         (c) 1998 Engineering Info. Inc.
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File 347:JAPIO Oct 1976-1998/Sep.(UPDATED 981229)
         (c) 1998 JPO & JAPIO
?ds

Set     Items   Description
S1        459   (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICAL?)(3-
                N)SPONG?
S2        579   COMPRESS?(3N)SYMBOL?
S3      48535   (AUTO OR AUTOMAT?)(3N)(ID OR IDS OR IDENTIF? OR DATA? ?) OR
                 MACHINE?(3N)(READ OR READS OR READING? ? OR READAB? OR READE-
                AB? OR SCAN? OR INVENTORY OR INVENTORIES) OR BARCOD? OR (BAR -
                OR BARS OR BARRED OR BARRING? ?)(2N)(CODE OR CODES)
S4      78254   (ID OR IDS OR IDENTIF?)(2N)(SYSTEM? OR METHOD? OR PROCEDUR?
                 OR PLAN OR PLANS OR PLANNED OR PLANNING? ? OR CONSTRUCT? ?) -
                OR (READ OR READS OR READAB? OR READEAB? OR READING? ?)(3N)(D-
                EVICE? OR APP?? OR APPARAT? OR INSTRUMENT? OR EQUIP?)
S5        979   (READ OR READS OR READAB? OR READEAB? OR READING? ?)(3N)(C-
                ONTRIVANCE? OR INVENTION? OR IMPLEMENT? OR TOOL?)
S6       3705   SCANNER?(3N)(READ OR READS OR READING? ? OR READAB? OR REA-
                DEAB? OR INVENTORY OR INVENTORIES)
S7          0   S1 AND (S2 OR S3 OR S4 OR S5 OR S6)
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?show files
File  43:Health News Daily 1990-1999/Jan 06
         (c) 1999 F-D-C reports Inc.
File 129:PHIND(Archival) 1980-1998/Dec W4
         (c) 1998 PJB Publications, Ltd.
File 149:IAC(SM)Health&Wellness DB(SM) 1976-1998/Jan W1
         (c) 1998 Info Access Co
File 158:DIOGENES(R) 1976-1998/Dec W3
         (c) 1999 DIOGENES
File 187:F-D-C Reports 1987-1998/Dec W4
         (c) 1998 F-D-C Reports Inc.
?ds

Set     Items   Description
S1        228   (SURGER? OR MICROSURGER? OR SURGICAL? OR MICROSURGICAL?)(3-
                N)SPONG?
S2          0   COMPRESS?(3N)SYMBOL?
S3       2010   (AUTO OR AUTOMAT?)(3N)(ID OR IDS OR IDENTIF? OR DATA? ?) OR
                 MACHINE?(3N)(READ OR READS OR READING? ? OR READAB? OR READE-
                AB? OR SCAN? OR INVENTORY OR INVENTORIES) OR BARCOD? OR (BAR -
                OR BARS OR BARRED OR BARRING? ?)(2N)(CODE OR CODES)
S4       7480   (ID OR IDS OR IDENTIF?)(2N)(SYSTEM? OR METHOD? OR PROCEDUR?
                 OR PLAN OR PLANS OR PLANNED OR PLANNING? ? OR CONSTRUCT? ?) -
                OR (READ OR READS OR READAB? OR READEAB? OR READING? ?)(3N)(D-
                EVICE? OR APP?? OR APPARAT? OR INSTRUMENT? OR EQUIP?)
S5         90   (READ OR READS OR READAB? OR READEAB? OR READING? ?)(3N)(C-
                ONTRIVANCE? OR INVENTION? OR IMPLEMENT? OR TOOL?)
S6         39   SCANNER?(3N)(READ OR READS OR READING? ? OR READAB? OR REA-
                DEAB? OR INVENTORY OR INVENTORIES)
S7          4   S1 AND (S2 OR S3 OR S4 OR S5 OR S6)
?t s7/ti/all

 7/TI/1     (Item 1 from file: 149)
DIALOG(R)File 149:(c) 1998 Info Access Co. All rts. reserv.

Infectious medical wastes. (Council on Scientific Affairs report)


 7/TI/2     (Item 1 from file: 158)
DIALOG(R)File 158:(c) 1999 DIOGENES. All rts. reserv.

  INSPECTIONS LOOK FOR BROADER QUALITY PROBLEMS AT FIRMS


 7/TI/3     (Item 2 from file: 158)
DIALOG(R)File 158:(c) 1999 DIOGENES. All rts. reserv.

  WARNING  LETTER  (REGULATORY  LETTER) 1/20/95 TO LOUISIANA INDUSTRIES FOR
THE BLIND: SURGICAL SPONGES PP: 2.


 7/TI/4     (Item 3 from file: 158)
DIALOG(R)File 158:(c) 1999 DIOGENES. All rts. reserv.

  E-Z  PREP  TOPICAL  SOLUTION AND SPONGE STICKS (DESERET): APPROVAL LETTER
AND REVIEWS PP: 36.

?t s7/9/3,4

 7/9/3     (Item 2 from file: 158)
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titles and selected citations

00431765 DIOGENES RECORD NUMBER: 193761
WARNING LETTER (REGULATORY LETTER) 1/20/95 TO LOUISIANA INDUSTRIES FOR THE BLIND: SURGICAL SPONGES PP: 2.
DEVICE CLASSIFICATION: SURGICAL SPONGES.
COMPANY NAME: LOUISIANA INDUSTRIES FOR THE BLIND DELHI, LOUISIANA
SOURCE: FOI SERVICES FULL TEXT (FT).
PUBLICATION DATE: January 20, 1995 (19950120)
RECORD TYPE: Fulltext
WORD COUNT: 523 (Short)
DOCUMENT TYPE: REGULATORY ACTION (REG).
LANGUAGE: English

January 20, 1995

Mr. Perry Smith, Secretary
Louisiana Industries for the Blind
114 Church Street
Delhi, LA 71232

Dear Mr. Smith:

During an inspection of Industries for the Blind, 206 West First Street, Delhi, LA, on 11/21-23, 12/2/94, our Investigator determined that your firm manufactures surgical sponges. Surgical sponges are devices as defined by Section 201(h) of the Federal Food Drug and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

Objectionable conditions noted included: 1) failure to validate the gamma sterilization process, manufacturing processes, and packaging operations; 2) no written procedures for reworking devices or for re-sterilization; 3) no specifications for gauze thickness, sealer operating parameters, and seal width; 4) no positive pressure specifications in the environmentally controlled area; 5) no device history records of the packaging sealer parameters; 6) no review of device history records and in-process control records; 7) no calibration documentations; 8) no documentation or device history records that incoming labels are examined for identity and proofread for accuracy, and there is no designated person to inspect and release labels; and, 9) failure to follow the MIL STD 105E sampling plan.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. This may include seizure and/or injunction.

You should notify this office in writing, within 15 working days of receipt of this letter of the steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action can not be completed within 15 working days, state the reason for this delay and the time within which the corrections will be completed.

Your response should be directed to Richard D. Debo, Compliance Officer, U.S. Food and Drug Administration, 4298 Elysian Fields Avenue, New Orleans, Louisiana, 70122, telephone number (504) 589-7166. Should you have any

questions concerning the contents of this letter, or if you desire a meeting with the agency staff, do not hesitate to contact Mr. Debo.

Sincerely,

James E. Gamet
Acting District Director
New Orleans District

Enclosure: FDA-483

cc: George B. Payne, Executive Director
Industries for the Blind
206 West First Street
Delhi, LA 71232

LEF

7/9/4 (Item 3 from file: 158)
DIALOG(R)File 158:DIOGENES(R)
(c) 1999 DIOGENES. All rts. reserv.

← (looked to be a dud)

00067589 DIOGENES RECORD NUMBER: 81212
E-Z PREP TOPICAL SOLUTION AND SPONGE STICKS (DESERET): APPROVAL LETTER AND REVIEWS PP: 36.
FDA NO.: F89-28549
BRAND NAME: E-Z PREP
DRUG NAME: POVIDONE IODINE
COMPANY NAME: DESERET
DEVICE/DRUG NO.: 19382
SOURCE: FOI SERVICES FULL TEXT (FT).
RECORD TYPE: Fulltext
WORD COUNT: 9713 (Long)
DOCUMENT TYPE: DRUG (DRG). Freedom of Information Act Request
LANGUAGE: English
JULY 26, 1989
NDA 19-382
Mr. Charles J. Welle
Deseret Medical, Inc.
9450 South State Street
Sandy, Utah 84070
Dear Mr. Welle:

Reference is made to your New Drug Application (NDA) dated October 29, 1984, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for E-Z Prep (povidone-iodine) Topical Solution and Sponge Sticks.

Reference is also made to your additional communications dated June 3 and 9, August 8, September 30 and November 14, 1986, January 13 and 30, July 9, September 2, November 10 and December 10, 1987, March 24, April 19, May 4, June 21, July 12, August 5 and 9, September 7, October 6 and November 30, 1988, and April 26, June 2, June 16 and July 11, 1989.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL to the Food and Drug Administration (FDA) as soon as available. For administrative purposes this submission should be designated as an "FPL Supplement" to the approved NDA. Approval of this supplement by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,
Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Division of Anti-Infective Drug Products
Chemist's Review #2
Date Completed: 6/15/87
A.1. NDA 19-382
Sponsor: Deseret Medical, Inc.
9450 South State Street
Sandy, Utah
2. Product Names:
Proprietary: E-Z Prep
Non-Proprietary: povidone-iodine topical solution
3. Dosage Form & Route of Administration:
soln. topical approx. 1% available I2
0.5% minimum available iodine on surgical sponges.
4. Pharmacological Category and/or Principal Indication:
Antimicrobial surgical prep.
5. Structural Formula and Chemical Name(s): USP item
B.1. Initial Submission: (review #1 R.C. Bieneman 4/5/85).
2. Amendments: 1/30/87 (1/13/87)
3. Related Material: COPY DELETED! contains stability data for the solution.
C/D. Remarks/Conclusion: Labeling for the solution should be consistent with that for the COPY DELETED! in potency declaration.
Room temperature storage conditions should be listed on the labels.
Application is otherwise approvable from a manufacture and controls viewpoint.
John W. Taylor, Ph.D.

Division of Anti-Infective Drugs
April 5, 1985
NDA 19-382
Parke-Davis and Company
9450 South State Street
Sandy, Utah 84070
Proprietary Name: Povidone Iodine Topical Solution, U.S.P. (Formula 41)
Dosage Form and Route of Administration: Product is a liquid, packaged in bottles or absorbed into sponges, for topical application. (Product will be primarily marketed as components of surgical kits.)
Pharmacologal Category / Principal Indication: Povidone-Iodine is an antibacterial. The product will be used for patient prepping.

Structural Formula & Chemical Name: See U.S.P. for structure. Povidone-iodine is 2-pyrolidinone,1-ethenyl-homopolymer compounded with iodine.
Related NDA's etc. NDA 19-240, DMF COPY DELETED! DMF COPY DELETED! DMF COPY DELETED!
Remarks: These drug products have been marketed for approximately ten years either as non-sterile or self-sterile products. This application due to the sterilization by radiation COPY DELETED! is considered a new drug. Firm has shown that radiation sterilization produces a change in the available iodine to iodide ratio similar to the degradation caused by elevated temperature or aging.
Conclusions: Controls are adequate. Labeling will be reviewed separately due to the March 12 submission of additional labeling. Sponsor has committed to do stability studies on commercial batches and report the data. We feel that the 18 month expiry requested by the firm can be granted if the firm reports stability data into the Records & Reports requirement for the first two years.
Memo from HFN-322 on inspections is attached.
R.C. Bieneman Chemist HFN-815

Division of Anti-Infective Drugs
NDA 19-382
August 19, 1985
Parke, Davis & Co.
9450 South State Street
Sandy, Utah 84070
Proprietary Name: Povidone Iodine Topical Solution, U.S.P. (Formula 41.)
Dosage Form & Route of Administration: Product is a liquid, packaged in plastic bottles or absorbed into sponges, for topical application. (Product will be primarily marketed as a component of surgical kits.)
Pharmacological Category / Principal Indication:
Povidone-iodine is an antibacterial. This product will be used for patient prepping.
This review covers the submission dated August 5, 1985.
Remarks: This review covers the use of the facilities of COPY DELETED! to sterilize this product by radiation.
Conclusions: Memorandum from HFN-322 (compliance) indicates that the COPY DELETED! firm is operating within our Good Manufacturing Practice guidelines. Controls remain approvable.
R.C. Bieneman Chemist HFN-815

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
NDA 19-382 (Amendment dated 1/28/85)
Date Review Completed: 3/7/85
Applicant: Parke, Davis & Co. (Deseret Medical, Inc.), Sandy, Utah
Drug: Povidone-Iodine Topical Solution, USP (Formula 41)
Indication: Pre-operative skin preparation paint
Related Submissions: NDA 19-240 (Povidone-Iodine Scrub Sponge)

Preclinical Study:
14-Day Dermal Toxicity Study in Rabbits: (Study # 84 T-08022)
Lab Perf. Study:
Materials Tested: Iodophor solution (Formula #41) radiated (COPY DELETED!) and nonradiated, Formula #41 vehicle COPY DELETED!
Species, Sex & No. Animals: NZ white rabbit; M & F; 5/sex/group

Treatment Groups	Treatment Material	Dose (ml/kg)
I	vehicle - 5.0 Mrads	1.0

II Iodophor - 0.0 Mrads 1.0
III Iodophor - 5.0 Mrads 0.2
IV Iodophor - 5.0 Mrads 1.0
Route: Percutaneously on intact or abraded skin (no occlusion)
Duration & Frequency: Once a day (minimum of 6 hrs) for 10 days (2 wks)

Results:

General Observations: Lethargy in 1 rabbit (gp IV), isolated cases of ocular discharge (1 vehicle control, 1 gp IV) and loss of appetite in a few rabbits were noted.

Body Wt: There was no statis. sig. difference in the gp mean body wts of various gps. One F (gp II) lost approx. 26% of its original wt and appeared dehydrated by the end of the 2-wk period.

Dermal Observations: No. sig. findings

Mortality: None

Hematology: Statis. analyses for hematology parameters showed no sig. treatment effects in any group. Slight decrease in Hb content was noted in the gp II animals, compared to pre-treatment values.

Clinical Chemistry: An increase in serum K level and a decrease in the T3 level (compared to other gps) were seen in the gp II animals. However, statis. analyses did not reveal any sig. difference.

Organ Wt: No. sig. differences between or among gps tested.

Gross Pathology; Unremarkable. In gp IV, white focal areas in the liver were reported in 2 animals (1 abraded, 1 unabraded).

Histopathology: Various renal and/or hepatic lesions noted were attributed to either Encephalitozoon cuniculi and/or Eimeria stiedae infections. In the kidneys, chronic lymphocytic interstitial nephritis or vacuolation of proximal tubule cells with foci of mineralization of damaged epithelial cells was reported. The hepatic lesions associated with Coccidiosis were lymphocytic cholangiolitis with or without actual parasites in the bile duct epithelium with scattered granuloma formation.

Evaluation & Comments:

In this 2-week dermal toxicity study, neither irradiated nor unirradiated PVP-I solution showed any significant adverse effects in rabbits. Microscopic examinations of adrenal and thyroid glands were within normal limits. Serum T3 level (group mean) was somewhat lower in the unirradiated PVP-I group when compared to the other gps, but the decrease was not significant. The study was performed as per our discussion with the applicant in a meeting held at FDA on 5/3/84.

This fulfills the preclinical safety study requirements for this NDA. The review of NDA 19-382, which had been submitted earlier, will be completed soon.

Syed N. Alam, Ph.D.

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-382 (Original Submission, dated 10/29/84)

Date Review Completed: 3/28/85

Applicant: Parke, Davis & Co., Sandy, Utah

Drug: Povidone-Iodine Topical Solution, USP (Formula 41), 10% iodine

Active Ingredients: Povidone-Iodine (PVP-1)

Chemical Structure:

***HARD COPY ONLY

Composition: % wt/wt

COPY DELETED!

Clinical Indication: Surgical preoperative skin preparation (radiation sterilized material)

Related Submissions: NDAs 19-240 (PVP-I Surgical Scrub Brush/ Sponge), 17-452/S-001, and 10-299 (Betadine); INDs COPY DELETED!

Preclinical Studies:

A. Effects of COPY DELETED! Radiation on Iodine in PVP-1 Solution:

1. A Study of the Potential Effects of COPY DELETED! Irradiation Sterilization on Topical Antimicrobial Solutions Present in the PVP-I Detergent (Formula 41):

Lab Perf. Study:

Material Tested: Formula 41 (PVP-I sol'n) with or without contact materials. Methods: PVP-I sol'n alone, PVP-I + Handle/Pouch Sponge, PVP-I + Bottle/Cap were irradiated at 0, 2.5 or 10 mrad with COPY DELETED!. The amounts of available and total iodine were determined in these samples and compared with the values obtained from non-irradiated materials. COPY DELETED! methods were used to determine organic breakdown products, if any, in these samples.

Results: In the PVP-I sol'n alone (without contact materials such as handle, pouch, sponge, bottle & cap), the available iodine decreased from a value of 1.11% in the non-irradiated samples to a value of 0.68% in the 10 mrad samples, while total iodine values remained unchanged in all samples. In the case of the sol'n in contact with handle/pouch/sponge, available iodine decreased from values of 1.05% in the non-irradiated samples to 0.61% in the 10 mrad samples, while the total iodine values again showed no statis. difference. The sol'n in contact with bottle/cap, after 10 mrad irradiation, had iodine content similar to the sol'n alone values.

No organo-iodine compounds were determined at the 50 ppm level in the COPY DELETED! analysis. In COPY DELETED! GC columns, analysis of COPY DELETED! an intermediate in the manufacture of PVP, represented the only peak obtained. This compound was present in all samples, irradiated & non-irradiated. The levels of COPY DELETED! appeared to decrease as the irradiation level was increased.

Analysis of the COPY DELETED!/mass spectrometry data indicated that no sig. changes occurred with radiation treatment of the materials. Computer searching of all spectra obtained from COPY DELETED! the spectral library for the presence of carcinogens and "certain" toxic substances was negative.

B. Toxicology:

1. Skin Sensitization Test with COPY DELETED! irradiated iodophor sol'n (5 MRAD):

Methods: The procedure described by Buehler in the Archives of Dermatology 91:171, 1965 was followed. The test liquid was placed on shaved backs of albino guinea pigs (10) under occlusion and after 6 hrs the test sites were evaluated. The test liquid was applied 3x/wk for a total of 9 applications. The animals were challenged (dermally) 2 wks after the last application of the test material.

Results: Both the sensitization and challenge scores for erythema and edema were zero.

2. Skin Sensitization Test with Non-irradiated Iodophor Solution: This study was performed in albino guinea pigs by methods similar to that used for irradiated material. Sensitization scores as well as challenge scores for erythema & edema were zero.

3. Primary Skin Irritation Test in Rabbits:

Material Tested: COPY DELETED! irradiated (5.0 mrad) iodophor sol'n

Methods: The material was applied on clipped dorsal trunk of each animal (abraded & unabraded) under occlusion for 24 hrs. After removal of the gauze pads, the test sites were scored for irritation at 24 & 72 hrs.

Results: The primary irritation score for combined abraded and unabraded skin was 0.043.

4. Primary Skin Irritation Test with Non-irradiated Iodophor Sol'n in Rabbits: The methods used in this study was the same as that used with irradiated material. The primary irritation score in this case was also 0.043.

5. Ocular Irritation Study in Rabbits:

Material Tested: Irradiated (5.0 mrad) & non-irradiated iodophor sol'n

Methods: Six albino rabbits were used for each test sample. The test material (0.2 ml) was placed in the left eye and the right eye was used as the control. Observations on the eye were made at 24, 48 & 72 hrs after instillation of the material.

Results:

Irradiated Material: Slight-moderate redness & swelling of the eye was noted in all 6 rabbits at the 24-hr reading. Corneal opacity & iritis were not observed. At 72-hr reading, the redness & swelling had decreased from moderate to slight.

Non-irradiated Material: Slight-marked redness & swelling of the eye was noted in all treated rabbits at the 24-hr reading. No corneal opacity or iritis was noted. At the 72-hr reading, the redness & swelling had decreased to moderate-slight categories.

6. Vaginal Mucosal Irritation in Rabbits:

Material Tested: Irradiated (5.0 mrad) & non-irradiated iodophor sol'n

Methods: Six albino rabbits were used. 0.1 ml of the test material was instilled into the vagina by means of a tuberculin syringe. Observations of the vagina for redness & swelling were made at 24, 48 & 72 hrs after treatment.

Results:

Irradiated Material: At the 24-hr reading, slight erythema was observed in 4 rabbits. By 72 hrs, all of the rabbits had normal appearing vaginas.

Non-irradiated Material: At the 24-hr reading, a slight erythema was observed in 3 rabbits. All of the rabbits had normal appearing vaginas at the 72-hr reading.

C. Microbiology: In Vitro Bacterial Efficacy of Formula #41:

Non-Irradiated:

Bacterial Strains Used: Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, Escherichia coli, Streptococcus pyogenes, Staphylococcus epidermidis.

Dilutions of Materials Tested: Full strength (FS), 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 & 1:128

Sampling Times: 1, 2, 5 & 10 min.

Results: Except for S. aureus & P. aeruginosa kill time was 1 min. at all dilutions. For S. aureus, kill time was between 1 & 2 min. & for Pseudomonas it was 1 min. at all dilutions except 1:32, for which a 2-min. kill time was reported.

2. Irradiated:

a) COPY DELETED!-irradiated (2.0 mrad)

Bacterial Strains Used: S. aureus, P. aeruginosa, E. coli, Candida albicans, Strep. pyogenes & Micrococcus luteus

Dilution of Material Tested: Full strength (FS), 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 & 1:128

Sampling Times: 1, 2, 5 & 10 min.

Results: Kill time was 1 min. for all organisms at all dilutions of the test material except 1:64, for which a 10-min. kill time was reported for P. aeruginosa.

b) 5.0 mrad:

This study was performed in the same way as above, the only difference being the use of Staphylococcus epidermis instead of Micrococcus luteus.

Results: The kill time increased to 5 min. with S. aureus and to 2 min.

for S. epidermidis.

Evaluation

This "paper NDA" has been submitted pursuant to the notice published in the Federal Register, Vol. 46, 0.27396, May 19, 1981. The applicant has proposed to market PVP-I (about 9%) topical sol'n USP (Formula 41) as a radiation sterilized surgical preoperative skin painting to reduce bacteria found on the patients' skin. The solution may be packaged with a sponge stick applicator or it may be packaged in bottles. The terminal sterilization will be achieved by COPY DELETED!. Minimum available iodine has been claimed to be 0.5%.

The applicant's efforts to establish safety of the product has primarily been to demonstrate that irradiation did not significantly change the chemical composition of the non-irradiated material. The only sig. change in the irradiated samples (2.5 or 10 megarad treated) was a dose-related decrease in the available (free) iodine, while the total iodine values remained unchanged in all samples (see also the Chemist's Review). The decrease was due to conversion of some iodine to iodide, a reaction that takes place also in non- irradiated material with passage of time. Usual "overage" of available iodine in the formulation should solve this problem.

The applicant has performed a limited number of acute toxicity tests with the irradiated PVP-I solution. Irritation tests indicated that the material was a slight skin irritant, "moderate to marked" ocular irritant and "slight to marked" vaginal mucosal irritant in rabbits. The non-irradiated material also showed similar irritancy except for vaginal mucosa, where it was rated as a "slight to moderate" irritant. Neither material showed any skin sensitization potential in guinea pigs.

No subchronic or chronic toxicity studies have been performed with the irradiated material. In a meeting with the applicant held at FDA on 5/3/84 (see memo, dated 5/3/85), it was decided that, since the drug will be used only occasionally on any particular patient as skin painting, a 2-week dermal toxicity study in rabbits (abraded & nonabraded skin) with the irradiated material would be satisfactory for establishment of safety of the drug. For comparison, the applicant was advised to include a group of animals for treatment with the non-irradiated PVP-I also. Such a study has been performed by the sponsor, and was submitted as an amendment to this NDA (dated 1/28/85) and have been reviewed (Pharm. Rev. dated 3/7/85). Except for somewhat lower serum T3 level in the unirradiated PVP-I group, no significant adverse effects were seen in any treated groups compared to the vehicle control group.

The safety of non-irradiated PVP-I has been examined by FDA Advisory Review Panel on OTC Antimicrobial Drug Products (I & II). The Panels examined voluminous data submitted by the manufacturer of PVP-I and various pharmaceutical companies who market this OTC product. Some of these data have also been submitted in this NDA. The first Panel's report was published in Federal Register, Vol. 43, page 1220, 1978. Based on this report, the Commissioner had ruled that PVP-I should remain in category III for OTC drug products. Since then the second Review Panel's report concluded that the drug was safe for most topical uses except for use on mucous membranes of the mouth & throat. The relevant proposed monographs have been published in Federal Registers: Vol. 47, #56, p. 12545, 1982; Vol. 47 #101, p. 22822, 1982; Vol. 47, #233, p. 54679, 1982; Vol. 48, #199, p. 46705, 1983. It is noteworthy that none of these indications, except for oral mouthwash and perhaps vaginal douche, envisions chronic usage.

The applicant has not performed any reproduction, mutagenicity or carcinogenicity studies with the drug. Although the Panels did not specifically mention it, two studies by COPY DELETED! in rats & rabbits indicated that Povidone itself was not teratogenic (Vol. 1.5, pp. 14-15). Woldkowski, Speck & Rosenkrank (Genetic Effects of Povidone Iodine, J. Pharm. Sci. 64: 1234, 1975) have indicated that PVP-I is cabable of altering DNA in living cells and inducing mutations in Salmonella. These

effects have been ascribed to the iodine. Other studies have refuted these results and the Panels concluded that there was no demonstrable mutagenicity or carcinogenicity associated with PVP-I.

The promotional labeling has not been made available yet. Since the applicant has no plan for any package insert (Telcon with Mr. Chuck Willey), the package label should mention the concentration of PVP-I in the solution.

Recommendation: On the basis of the safety data provided for this NDA, I find the application approvable.

Syed N. Alam, Ph.D.

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDAs 19-382*

APPLICANT: Deseret Medical, Inc., Sandy, Utah

DRUG: *Povidone-Iodine Topical Solution, Formula 41

CATEGORY: Antibacterial

INDICATION: Patient pre-op skin preparation

PRECLINICAL STUDY

Delayed Contact Dermal Sensitization Test in Guinea Pigs

Lab Perf. Study:

Material Tested: Formula 41 (Povidone Iodine Topical Sol'n Irradiated

Species: Albino guinea pigs (M & F)

No. Animals: 5/sex/group and controls

Methods: The material (0.3 ml) was applied under occlusion to clipped flanks of the g-pigs for 6 hrs/day, 3 days/week for 3 weeks. After a rest period of 2 weeks, the animals were challenged dermally with the test materials.

Results: During the induction phase of this study, dermal irritation was observed at the treatment sites of the positive control group. No irritation was observed at the test article treatment sites during the induction phase.

Following the challenge patch application, no dermal reaction was observed in the animals patched with the test article or in the negative control groups challenged with the test article or DNCB (positive control).

EVALUATION

All 3 submissions are the result of deficiencies in the Original NDA submission. In pharmacology, a guinea pig sensitization study submitted in support of this NDA had to be rejected later because the Div. of Scientific Investigation discovered serious deficiencies (GLP) at the control laboratory. The applicant had the study repeated at COPY DELETED!. The results, as reviewed above, indicate that Formula 41 is not a sensitizer in guinea pigs under the conditions of the experiment.

From the preclinical safety standpoint, I find no problem with this NDA and consider it to be approvable.

Syed N. Alam, Ph.D.

April 16, 1985

Clinical Review of NDA 19-382

Sponsor: Parke Davis and Company

Sandy, Utah

Drug: E-Z Prep (povidone-iodine) Topical Solution

Formulation: COPY DELETED!

Category: Surgical preoperative skin preparation

Date of Submission: October 29, 1984. Amendment dated January 12, 1985.

Related Submission: NDA 19-240, Povidone-iodine in a scrub sponge.

Pharmacology and Controls Review: The chemist, Mr. Bieneman, has found this application to be approvable. The pharmacologist, Dr. Alam, has completed a preliminary review of this application and promises a final review soon.

Background: Povidone-iodine has been used as a topical antimicrobial agent for many years. The standard for this type of product is Betadine, which contains 10% povidone-iodine. The sponsor of this NDA proposes to market a kit which contains a bottle of 10% povidone-iodine solution (equivalent to 1% available iodine), 5 and 8 inch long urethane sponges saturated with the same solution, and unsaturated sponges which may be saturated with the furnished bottled material prior to use. This kit is to be sterilized by COPY DELETED! irradiation COPY DELETED! which requires that the products be designated as new drugs under 21 CFR 200.30. In addition, the sponsor has determined that the irradiation procedure as well as interaction between the urethane sponges and the povidone-iodine solution causes the available iodine in the factory saturated sponges to drop to approximately 0.5%. For this reason, a study to evaluate the activity of the pre-saturated sponges against the normal microbial flora of the skin was performed. It should be noted that products of the povidone-iodine type were placed in Category III (needs more study) by the proposed Topical Antimicrobial Products monograph. In the meantime, FDA has not acted upon products of this type pending publication of the final monograph. The Regulations require a new drug application for the product, and we find no reason not to approve it since safety and effectiveness can be shown.

Ms. Lee Geismar of the OTC Division was contacted to find out whether that group would have any objection to approval of this NDA under the above circumstances. She stated that there would be no objection as long as it is understood that approval of this specific product would have no bearing on the conclusions published in the final monograph.

Clinical Effectiveness Study

Investigator: Arthur Peterson, Ph.D.
Skyland Scientific Services, Inc.
Belgrade, Montana

Method: Thirty-one subjects of both sexes were tested. Three sampling areas were tested: the forehead, groin and abdomen. Baseline samples of the resident microbial flora were taken, with only those subjects who showed a 3 log10 or greater abdomen baseline value and/or 4 log10 or greater forehead and groin baseline values being evaluated.

The irradiated prepared sponges were tested against the non-irradiated prepared sponges. The non-irradiated sponges are not an acceptable control group, since FDA has not officially evaluated povidone-iodine as safe and effective for use as a patient preoperative preparation. However, there is another absolute method of defining effectiveness given in the Tentative Final Monograph for OTC Topical Antimicrobials. The monograph states that patient pre-operative preparations should produce a 3-log reduction in flora in 30 minutes or less. We are in agreement that this absolute standard is prudent.

The test procedure was as follows: 15 subjects received the irradiated product and 15 the non-irradiated product. The area to be treated was swabbed for 15 seconds. Sampling was done 10 minutes later. Bandages were then applied to the treated areas. Additional samples were taken 30 minutes and 4 hours after application.

Results: The results for the irradiated product only are presented.

Mean Log10 Reductions on Three Sites

Time Interval	Forehead	Abdomen	Groin
10 min.	.80	2.77	3.25
30 min.	1.41	3.33	3.93
4 hours	1.33	2.93	3.50

The data for the groin reduction is acceptable. We can also accept the abdomen data given the fact that baseline values had only to be 3 log10 or

greater. However, the data for the forehead reduction is unacceptable. In the absence of an acceptable control group, we are unable to evaluate the significance of this lack of activity.

Labeling Review: A complete labeling review will be performed when the application is complete in other respects. However, two preliminary comments are as follows: the products must be designated as "patient preoperative skin preparations" rather than as "paint solution", etc., and the amount of available iodine must be declared on each piece of labeling.

Evaluation and Conclusions: This application may not be approved. The study for reduction of the microbial flora of the forehead should be rerun with the test product being evaluated against an approved product for patient preoperative prepping such as Hibiclens.

David C. Bostwick
C.C. Evans, M.D.
February 4, 1986

Clinical Review of NDA 19-382
Sponsor: Parke, Davis & Company
Sandy, Utah
Drug: E-Z Prep (povidone-iodine) Liquid and Sponges.
Category: Patient preoperative skin preparation
Date of Submission: October 29, 1984. An amendment dated December 19, 1985 has also been submitted and is the subject of this review.
Related Submission: NDA 19-240, Povidone-iodine in a scrub sponge
Pharmacology and Controls Reviews: These are approvable.
Background: Please see our previous review of this NDA dated April 16, 1985 and the "not approvable" letter of August 29, 1985.

Material Reviewed: Our not approvable letter stated that a second clinical study by another investigator would be necessary prior to approval. We have since revised our policy for topical antimicrobials to require only one study for well-known chemicals and standard indications. However, the study submitted with the original application was inadequate in that one of the test sites (the forehead) did not display the 3-log reduction specified by the OTC Antimicrobial Monograph. We recommended that sponsor retest the forehead site using an approved patient preop product as a control.

The sponsor has therefore submitted a study of E-Z Prep vs. tincture of iodine U.S.P. in reducing the normal microbial flora of the forehead. The test procedure followed was much the same as was done in the first test, with the addition of a group tested with tincture of iodine. The raw data was not submitted with the amendment. The results as presented by the sponsor are as follows (12 patients were treated with tincture, and 17 with E-Z Prep):

Mean Log10 Reductions on Forehead

Time Interval	Irradiated E-Z Prep	Tincture of Iodine
10 min	4.74	3.49
30 min	4.55	3.64
40 hrs	4.00	4.28

It can be seen that the E-Z Prep product is at least as effective as the tincture of iodine in decreasing bacterial counts. Part of the reason for this superiority may be that the mean at baseline for the tincture was 4.77 log10 while the baseline mean for E-Z Prep was 6.27 log10. The investigator states that the test subjects were extremely variable in microorganism counts, which made randomization difficult. We are nonetheless satisfied that E-Z Prep is at least as effective as a patient pre-op as is the tincture of iodine preparation approved through the OTC Monograph procedure. The raw data (log10 counts) should be submitted in order to complete our files.

Labeling Review: The following comments concerning the labeling are pertinent:

1. The amount of available iodine should be placed in conjunction to the large "povidone-iodine" connected to the trade name, thus:
E-Z Prep (povidone-iodine)-1.0% available iodine-Topical Solution.
2. The Directions should reflect the conditions used in the testing. In this case, the directions should read, "Swab the surgical site with E-Z Prep for at least 15 seconds and dry."
3. A statement concerning recommended conditions of storage should appear on the label.

Evaluation and Conclusions: This application may be made approvable with the recommended labeling changes and submission of raw data for the forehead test procedure.

David C. Bostwick
C. Carnot Evans, M.D.
March 27, 1986

Clinical Review of NDA 19-382
Sponsor: Parke, Davis & Company
Sandy, Utah
Drug: E-Z Prep (povidone-iodine) Liquid and Sponges
Category: Patient preoperative skin preparation
Date of Submission: October 29, 1984. Amendments dated February 12, 1986 and April 23, 1986 have also been submitted and are the subject of this review.

Background: See previous reviews of this NDA dated April 16, 1985 and February 4, 1986 and the "not approvable" letter of August 29, 1985.

Material Reviewed: In our last review, we noted that the raw data for the test of the forehead site (second test) had not been submitted. This data is now available in the February 12, 1986 submission. As was noted in ourreview of February 4, 1986, the mean log10 count at baseline for the E-Z Prep group was 6.27, while the mean for the tincture of iodine group was 4.77. There was some concern that this discrepancy could have influenced the test results in favor of E-Z Prep.

The sponsor has submitted a table which expresses the reductions in bacterial counts as log10 for those patients who were treated with tincture of iodine (patients #15-26) and those treated with E-Z Prep (irradiated povidone-iodine, patients 27-43). We have noted the Division Director's comment concerning our February 4, 1986 review which deals with the question of whether the higher mean baseline counts in the E-Z Prep group biased the results in E-Z Prep's favor. These results are interesting in that respect. Three of the 12 patients (25%) treated with tincture of iodine failed to reach the guideline 3- log reduction in organisms at the 10 minute interval. The baseline counts for these patients were 6.4, 3.2 and 5.6 log10. Four of the 17 patients (24%) treated with E-Z Prep failed to reach a 3-log reduction in the same interval. The baseline counts for these patients were 6.1, 3.6, 7.1 and 4.4 log 10. It does not appear from these data that the baseline count was critical to the amount of decrease in organisms attained.

One fact which does seem apparent is that the tincture of iodine patients were kept at a lower level of organisms longer than the E-Z Prep patients. This is especially noticeable in the 4-hour interval data. Since substantivity is not crucial to patient preop products, we do not consider this phenomenon to be a reason to disapprove the application.

We note the Division Director's request for a second study to substantiate the results of the first. We have no strong feelings either way on this subject, but we do offer the following justification for our willingness to rely on one study:

1. Research indicates that previous patient preop applications (e.g. Hibiclens) have been approved on the strength of studies of the axilla and

abdomen only. The forehead data was generated at the option of the sponsor. A case could be made that the repeat forehead study constitutes the required second study.

2. Apparently 0.5% available iodine in a povidone-iodine product will be approved when the final OTC Topical Antimicrobial Monograph is published.

Labeling Review: The Directions for use are now satisfactory. The conditions of storage should specify a temperature range. Comment #1 in our labeling review of February 4, 1986 is still pertinent.

Evaluation and Conclusions: In our opinion, this application may be made approvable.

David C. Bostwick
C. Carnot Evans, M.D.
NDA 19-382
June 26, 1986
Division Director's Memorandum

This New Drug Application (NDA) for E-Z Prep (povidone iodine) Liquid and Sponges should not be approved, for the reasons outlined in my comment of February 19, 1986. In this regard, I have carefully considered the arguments in the Clinical Review of March 27, 1986. Specifically:

1. The mean bacterial count at onset was higher in the E-Z Prep group than in the tincture iodine group. A higher concentration of organisms could have biased the study in the following ways:
   a. decreased availability of nutrient could have made the organisms more susceptible to killing;
   b. the mean reduction could have been achieved with different kinetics than with fewer organisms, because of the greater density of organisms.

   In addition, it suggests lack of proper randomization of study subjects.

   Even the greater mean reduction in the E-Z Prep group does not fully compensate for this possible bias.

   With regard to the arguments in Mr. Bostwick's Clinical Review of March 27, 1986, second paragraph under "Material Reviewed," the fact that failures in both groups have roughly equal low mean counts at onset (5.1 for tincture of iodine; 5.3 for E-Z Prep) does not alter the potential bias. In fact, this supports the concern about bias, since most of the E-Z Prep subjects with high mean counts at onset are among the successes.

2. I do not feel any modification of the requirement for two studies can be made in this case. However, I think the submitted study can serve as one of those studies if the second study shows a clear cut effect of E-Z Prep and no potential bias.

   Our policy of allowing approval of certain scrub products on the basis of one study as a bioavailability study has been limited to products with the same formulation and concentration as an approved product, and limited only to claims for surgical scrubs and health care personnel handwashes. E-Z Scrub meets neither of these conditions. It is a lower concentration (0.5%) than the approved product (1%) and thus its efficacy must be proven in one study and confirmed in a second study. In addition, it is the position of the Division that the patient pre-op claim has greater potential risk for the patient if an ineffective product were used; thus two studies should be submitted for efficacy for reasons of patient safety.

3. Raw data should be submitted for the first forehead-only study as well as the second.

4. Even if the forehead site was generated at the option of the sponsor, the fact that it failed to show efficacy at the forehead site in an earlier study makes that one study of groin, abdomen, and forehead unacceptable except in conjunction with the submitted forehead-only study.

5. The prospect of inclusion of 0.5% povidone iodine in the OTC Monograph does not change these issues, since that does not include the patient pre-op claim.

Edward Tabor, M.D.
NDA 19-382
Date Begun: August 19, 1988
Date Completed: January 23, 1989
Clinical Review of Amendments
Sponsor: Deseret Medical, Inc.
Sandy, Utah
Drug: NDA 19-382, E-Z Prep (povidone-iodine) Topical Solution and Sponge Sticks.
Category: Surgical preoperative skin preparation.
Dates of Submission: NDA 19-382 was originally submitted October 29, 1984. Numerous amendments have been submitted, the most recent on November 30, 1988.
Pharmacology Reviews: The pharmacologist, Dr. Alam, has no objection to the approval of these applications.
Chemistry Reviews: Dr. John Taylor found these applications to be approvable in 1987.
Background: Please see the following previous reviews and letters.

A. NDA 19-382. Clinical reviews dated April 16, 1985, and February 4 and March 27, 1986. Microbiology reviews dated September 6, 1985, February 27, 1986 and May 10, 1988. Not approvable letters dated August 29, 1985 and July 28, 1986.

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In brief, both these applications have one acceptable clinical study. The sponsor has had problems with performing a second study, primarily because it was difficult to find a patient population with a sufficiently high baseline bacterial count to achieve a 3-log drop in count as required by the OTC Topical Antimicrobial Products Tentative Final Monograph of January 6, 1978.

Additional Comments: The history of approval of these products is long and confusing. Our present standards for approval of a patient preoperative skin preparation are a combination of the standard set by the proposed OTC Topical Antimicrobial Monograph (basically, a 3-log reduction in baseline bacteria at two separate body sites), and the standard "well-controlled" study, which in this case is comparison to a product already approved as a patient pre-op.

We have not been able to identify the basis for the "3-log" standard for bacterial reduction set in the 1978 OTC Monograph. The Monograph does not give references justifying this standard.

To date, only one product has been approved through the NDA process as a patient pre-op. This is Hibiclens (NDA 17-768/S-002). A summary of the data which was involved in gaining approval for Hibiclens is interesting and is presented here:

Six studies were performed in support of the preoperative skin preparation indication. These studies may be grouped as follows (each study involves 50 patients):

A. Abdominal and umbilical sites:

1. David Taplin and Harry Blank, M.D. A study in which the abdomen was divided into quadrants and a pre-treatment sample, 10-minute and 240-minute samples were taken. The pre-treatment count was too low to allow the minimum 3-log reduction in bacterial count considered necessary by FDA to establish effectiveness as a preoperative skin preparation. A fraction of the patients also had the umbilicus sampled and a 3-log reduction was not attained.
2. Peter Dineen, M.D. The protocol for Dr. Dineen differs from the above in that a sterile towel was taped over the shaved and washed site the night before scheduled surgery. This procedure may account for increased initial counts. In any event, greater than a 3-log reduction was found and

maintained at both sites by this investigator.

3. Mollie McBride, M.D. The protocol followed was identical to that of Drs. Taplin and Blank. Once again, the pre-treatment count at the abdomen was too low to allow the 3-log reduction. A satisfactory reduction was found and maintained at the umbilicus in this study.

B. Perineal, groin and vaginal sites:

1. Stanley Birnbaum, M.D. A study in which samples were taken of the groin, perineum and vagina prior to preoperative preparation in predelivery patients and at 10 and 30 minutes after preparation (groin and perineum). The vagina was sampled 10 minutes after preparation only. A 3-log reduction was found and maintained at all three sites.

2. Helmuth Vorherr, M.D. A study identical to that of Dr. Birnbaum. A 3-log reduction was found and maintained at all three sites.

3. Mollie McBride, M.D. Dr. McBride sampled only the groin and perineum in her study. A 3-log reduction was found and maintained at both sites.

It can be seen from this data that it has historically been difficult to achieve a 3-log reduction in bacteria at the abdomen site simply because the test subjects do not typically have a high enough baseline count to make this practical. If Hibiclens were under consideration at the present time as patient pre-op it would not be approved because the abdomen counts were not high enough to permit a 3-log reduction. The only abdomen test which produced a 3-log reduction involved a towel over the test site the night before the baseline counts were taken, which probably produced artificially high levels of bacteria. Deseret has also had difficulty in finding patients who are "dirty" enough to test at the abdomen site.

There is also another criticism of the 3-log reduction standard. If a patient has an unusually high baseline bacterial count, it is possible that the 3-log reduction would still leave him (or her) with sufficient bacterial counts to make surgical incision dangerous. There has been discussion with the Division about using a different type of criterion for testing of this type. One suggestion is to use a "limit of the method" type of test which would require that bacteria be reduced to levels which are at the lower limit of available testing methods. This method has the advantage of assuring that low levels are reached. However, this method has not been tested.

An alternative to this type of testing is the "classic" study which is controlled by a placebo or active control. It is felt that simple superiority to a placebo is insufficient evidence of effectiveness for an indication that is so important to the safety of the patient. We have, therefore, required that the control for these povidone-iodine products be tincture of iodine, which is classified as "Category I" in the proposed OTC Antimicrobial Monograph.

Material Reviewed:

A. Concerning standards for patient pre-ops as a class

On December 15, 1988, Drs. Bilstad, Gavrilovich, Evans and Weissinger and Mr. Bostwick and Mr. Sheldon met to discuss these issues. This group discussed the issue of whether a placebo group is necessary to do the "new" (limit of the method) test, and agreed that it is not. Dr. Nevius is working on the problem of the number of patients needed to achieve statistical significance in the new test. It was agreed that the new test is promising and will probably solve the problems which the old evaluation method displayed.

The discussion then turned to the approvability of NDA's 19-382 COPY DELETED!. It was then noted that while the applications are not approvable under the 3- log reduction test, it is possible that they could be approved under the conditions set in the revised Tentative Final Monograph for

topical OTC antimicrobials. This monograph lowered the requirement for log reduction to 2 logs from 3 logs. If ODE II personnel agree with the data in the monograph which support the new criteria, the Deseret product could be re-evaluated for 2 log reductions.

We have therefore researched the monograph and obtained the pertinent references. In addition to commonly available in vitro data, two studies were cited, as follows:

1. Joress, S.M., "A Study of Disinfection of the Skin: A Comparison of Povidone-iodine with Other Agents Used for Surgical Scrubs", Annals of Surgery, 155:296-304, 1962. In one portion of this study, 25 volunteers were tested with a control and six active products, including Betadine Antiseptic and Betadine Surgical Scrub. Like most Betadine products, these contain 10% povidone-iodine or about 1% available iodine. The anterior surface of the forearm was used as the test site. Cultures were taken prior to scrubbing. The Betadine products were tested as follows:

A. Betadine Antiseptic. The skin was cleansed with soap and water, rerinsed, and wiped for one minute with a gauze sponge soaked in the product. This was allowed to dry, and cultures were taken (exact times not specified). The results indicated that in the 25 subjects with initial counts of 210-600 bacteria/sq. inch of skin, 21 showed no bacteria after cleansing by the test method employed, while the other 4 had 1-2 bacteria per sq. inch.

B. Betadine Surgical Scrub. The skin was scrubbed for 5 minutes with the product, rinsed with water and dried with sterile towels. In the same 25 subjects, 19 exhibited no bacteria after cleansing, while the other 6 had 2-5 bacteria/sq. inch.

In a second portion of the study, 40 patients undergoing general surgery were tested with Betadine Surgical Scrub. The skin preparation consisted of a five- minute scrub at the surgical sites (not specified) followed by rinsing with sterile water and drying with sterile towels. In each case, the skin was cultured before and immediately after the skin preparation, and at the end of the operations which lasted from 15 minutes to 3 hours. Eight of the 40 patients exhibited prescrub counts of 100 or more organisms/sq. inch of skin. All of these patients except one had no bacteria present after the scrub or operation by the culturing methods used. The one exception began with 36,000 bacteria/sq. inch and ended the scrub with 3 per sq. inch. The OTC Monograph tabulates these data as 1.78 log reduction immediately after prepping and 1.80 log reduction following the operations. Seventeen other subjects had baseline counts of 3 to 65 organisms per sq. inch and were presumably included in these averages.

2. Dunignan, N.M., and Lowe, P.A., "Pre-operative Disinfection of the Vagina", Journal of Antimicrobial Chemotherapy, 1:117-120, 1975. In this study, performed in England, vaginal aspirates were collected from 84 pre-operative patients before and after preparation of the vagina with disinfectant solutions. Among solutions tested was Betadine Surgical Scrub dilutes 1:10. The authors note that this solution then contained 0.075% available iodine, although the product marketed in the U.S. would have 0.1% available iodine if diluted 1:10.

Other solutions were tested, but 35 patients were tested with the Betadine dilution. A sterile speculum was introduced into the vagina and 0.5 ml of sterile saline placed in the posterior fornix; 0.1 ml was then aspirated in a separate pipette and placed in thioglycollated broth. The vagina was cleansed with diluted Betadine, which was left in place for 1-3 minutes before being removed. A second vaginal aspirate was then collected.

The results indicate that Betadine removed 92% of the pathogens present.

The references reviewed do not provide an ideal basis for a decision to make the criterion for approval of a patient preoperative skin preparation a 2- log reduction in baseline microbial count. The second reference, because of the methodology employed, is not directly applicable to the classic methods of preparing a patient's skin for surgery. However, in our

opinion, the first reference (Joress) does satisfactorily establish that 10% povidone-iodine will produce at least a 2-log reduction in baseline flora when properly used. We feel that the forearm testing in the Joress paper, in which the test products were used in a consistent manner on a similar test site in the same 25 patients is actually more persuasive than the testing done in surgical patients because the test sites for the surgical patients were not specified and there were relatively few patients with at least a 2-log baseline count. In both tests, however, the povidone-iodine product did in fact produce at least a 2-log reduction.

Recommendations: We recommend acceptance of the 2-log reduction in baseline bacterial counts for the following reasons:

1. As outlined in "Additional Comments" above, the original 3-log reduction criterion is not supported by practical experience (nor is it supported in the literature, as nearly as we can determine).

2. The 2-log reduction is supported by the literature. This is somewhat of a "which came first" situation, however. By this, we assume that since literature was available to support a 2-log reduction, the OTC Monograph adopted this standard. This does not speak to the question of the activity which an ideal patient pre-op would have, but rather adopts a criterion which is supportable. It is not clear to us whether anyone has previously considered what a patient pre-op should do, rather than what it can do. We therefore support further development of the "limit of the method" type of test mentioned above.

B. Concerning the specific NDA COPY DELETED!

With these comments in mind, we have re-analyzed the efficacy data available for these two applications. The majority of these analyses were performed using Mr. Sheldon's microbiology reviews (see "Background" above) as reference.

1. NDA 19-382. The original study performed by COPY DELETED! in 1985 produced acceptable (3-log) reductions at the abdomen and groin sites at 10 minute and 30 minute test intervals.

A second study performed by COPY DELETED! was submitted in September, 1987. This test compared Deseret's irradiated and non-irradiated povidone-iodine with tincture of iodine. The data in this study are unusual in that the baseline for the abdomen test site is higher than that for the groin test site (Mr. Sheldon speculates that the inguinal area was not properly tested). In any event, the data may be summarized as follows (all scrub times in these tests were 15 seconds):

Microbial Counts (Log10) at Baseline and Sampling Intervals

Site/Sample Interval	Count (Reduction) Tincture of Iodine	Count (Reduction) Irradiated Sponge Stick
Abdomen/Baseline	2.198	2.083
10 minutes	0.202 (1.996)	0.208 (1.875)
30 minutes	0.228 (1.970)	0.150 (1.933)
Groin / Baseline	2.015	2.053
10 minutes	0.155 (1.860)	0.288 (1.765)
30 minutes	0.212 (1.803)	0.109 (1.944)

These results indicate that povidone-iodine is comparable in bacterial reduction to tincture of iodine (a product which contains alcohol as well as more available iodine).

Since the low baseline counts made achievement of a 3-log reduction impossible, the sponsor had a third test performed by COPY DELETED!. This study was submitted on November 30, 1988. The data may be summarized as follows:

Microbial Counts (Log10) at Baseline and Sampling Intervals

Site/Sample Interval	Count (Reduction)	Count (Reduction)

	Tincture of Iodine	Irradiated Sponge Stick
Abdomen/Baseline	3.761	3.901
10 minutes	1.612 (2.149)	1.752 (2.149)
30 minutes	1.686 (2.075)	2.179 (1.722)
Groin / Baseline	4.815	4.955
10 minutes	1.854 (2.961)	2.784 (2.171)
30 minutes	1.174 (3.641)	2.218 (2.737)

The data from this study are both troubling and illuminating. COPY DELETED! screened 144 subjects in order to find 42 with sufficiently high baseline counts to allow a 3-log reduction. Even so, only one such reduction was reached (tincture of iodine at the 30-minute groin test site). It is further interesting to note that the povidone-iodine product decreased in effectiveness at the 30-minute abdomen site but increased in effectiveness at the 30-minute groin site. Further, while the COPY DELETED! did not detect much difference between the test products, the COPY DELETED! finds the tincture of iodine to be measurably more effective than povidone-iodine. We believe these effects to be due to the short scrub time used (15 seconds was used in all three tests described here). We believe that these results confirm Mr. Sheldon's impression that shorter scrub times may result in a lack of effectiveness for the product, and further, that a product with less active ingredient (such as the povidone-iodine product) may be more vulnerable to ineffectiveness due to short scrubs than more potent products, especially in patients with high baseline counts. We recommend that this product state in its labeling that a one-minute scrub is required for its proper use.

Recommendation: In view of our decision to accept the 2-log reduction standard (at least for the time being) as the principal criterion for effectiveness for patient pre-ops, we are prepared to recommend this product for approval. The COPY DELETED! studies may be accepted as the two necessary pivotal studies for this product. Although low baselines prohibited actual attainment of the 2-log standard in the COPY DELETED!, this level of reduction was nearly reached by the povidone-iodine product, and its effect was comparable to the more potent tincture of iodine.

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C. Labeling Review

1. NDA 19-382. In our previous "not approvable" letter for this NDA (dated July 28, 1986), we asked that the amount of available iodine in each dosage form be prominently stated. The sponsors have done this. The following additional labeling comments are pertinent:

a. As noted in the review of the clinical data, it is felt that a 1-minute scrub time should be recommended on the label.

b. The storage conditions on the label should be changed to "Store at Room Temperature" (see Chemist's review).

c. In order to standardize labeling for povidone-iodine products, the "Warnings" section should read the same as does the "Caution" section in NDA 19-522 (Povidone-iodine Topical Solution), which was recently approved. This section reads as follows:

Caution: For external use only: Do not apply to persons allergic to iodine. Not for ophthalmic use. Keep out of the reach of children. In case of accidental ingestion, seek professional assistance or consult a poison control center immediately.

d. The Indications section should read "For patient preoperative skin preparation."

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Conclusions:

A. Concerning patient pre-operative skin preparations as a class:

1. It is recommended that the 3-log reduction in baseline microbial growth be dropped as the primary requirement for approval of these products. As discussed under "Additional Comments" above, we have been unable to establish theoretical or practical grounds for this criterion.

2. We recommend acceptance of the 2-log reduction in baseline microbial growth proposed by the revised Topical Antimicrobial Drugs OTC Monograph as an interim standard. There is at least practical justification for this standard although it does have one weakness discussed under the discussion of the 3 log criterion. That is, if a patient has an unusually high baseline bacterial count, it is possible that a product which removed 2 logs of bacteria would still leave sufficient bacterial counts to make surgical incision potentially dangerous.

B. Concerning NDA 19-382

1. It is recommended that NDA 19-382 be made approvable with additional labeling changes. Two well-controlled studies by independent testing laboratories have established that this product is capable of achieving a 2-log reduction in baseline bacterial count or producing reductions in bacterial counts equivalent to the reference product, tincture of iodine. A third well- controlled study in patients especially selected to have high baseline indicated that neither tincture of iodine nor povidone-iodine was as effective as one would hope they would be. We believe that this indicates the need for relatively long scrub times.

David C. Bostwick
Chemist
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Group Leader
JUL 1 1989
NDA 19-382
Date Review Begun: July 11, 1989
Date Review Completed: July 12, 1989
Clinical Review of Labeling and Safety Update
Name of Drug: E-Z Prep (povidone-iodine) Topical Solution and Sponge Sticks
Sponsor: Deseret Medical, Inc.
Sandy, Utah
Date of Submission: June 2, 1989 and July 11, 1989
Indications: Patient preoperative skin preparation

Background: Please refer to our review dated August 19, 1988. That review contained several labeling suggestions which were informally given to the applicant during the period of negotiation of this NDA with Dr. Bilstad. On June 2, 1989, the sponsors submitted revised draft labeling which complied with our requests with one exception: We wanted the Directions to read as follows:

Apply locally to the surgical site with moderate pressure for at least one minute. Let dry.

The sponsor's proposed statement reads as follows:

Apply locally to skin with moderate pressure and prep for one minute.

Material Reviewed: In her review of the data for the product, the Division Director felt that since the commonly accepted standard for patient prepping, Hibiclens, has a two minute scrub time in its labeling, it would be prudent to require the same time for E-Z Prep. I called Mr. Charles Welle of Deseret to discuss these problems.

On July 12, Mr. Welle called back to say that Deseret would accept the two minute scrub time. In addition, since the pre-op kit that the drug comes in is equipped with a sterile towel, Deseret would prefer to modify the "Let dry" statement to read "Blot excess with sterile towel and let dry". I indicated that this statement is satisfactory to us. Mr. Welle then

sent revised draft labeling to us.

In addition, I asked Mr. Welle for a safety update on the application. He stated that there is no new safety information to report for either the irradiated or unirradiated products.

Conclusions and Recommendation: This application should be approved with draft labeling.